Natural Product Synthesis

Biomimetic Total Synthesis of Litseaverticillols A, C, D, F, and G: Singlet-Oxygen-Initiated Cascades**

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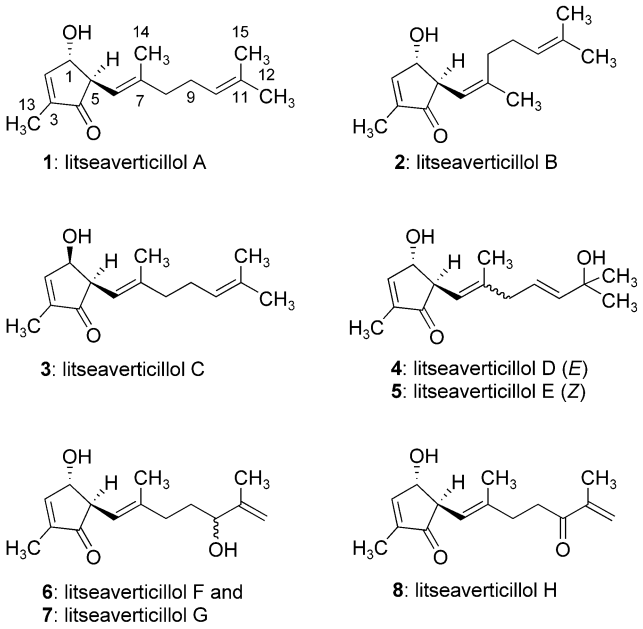
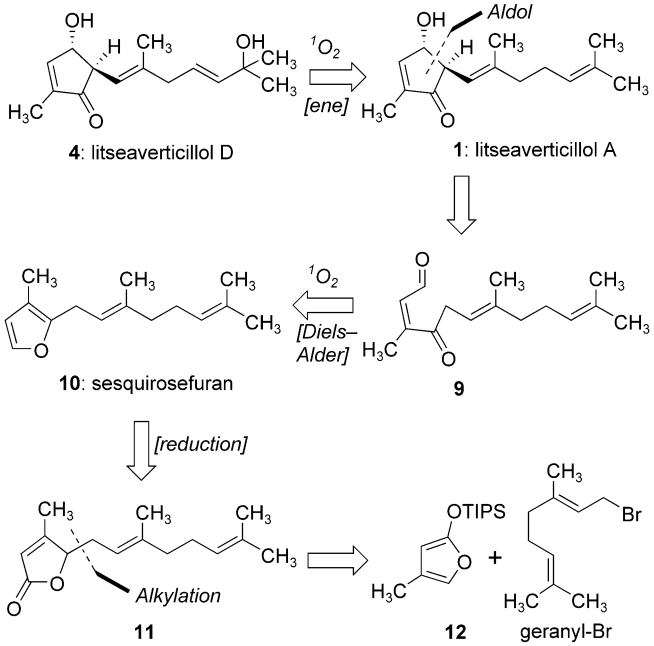
Dedicated to Professor Christopher S. Foote

The litseaverticillols (A–H, **1**–**8**, Scheme 1) are a recently isolated novel class of bioactive natural products. They were identified as the result of bioassay-guided fractionation of chloroform extracts from the leaves and twigs of a perennial shrub, *Litsea verticillata* Hance, found in Cuc Phuong National Park, Vietnam.[1] The eight new sesquiterpenes (**1**–**8**) were fully characterized because of their potent anti-HIV activity. More advanced biological studies revealed that compounds **1**–**8** inhibit HIV-1 replication in HOG.R5 cells (a reporter cell line)[2] with IC_{50} values (the concentration required for 50% inhibition) ranging from 2 to 15 μg mL^{-1} (8–85 μM). Furthermore, this viral inhibition was shown to be selective; HOG.R5 cell growth was only significantly affected at concentrations two- to threefold higher than the IC_{50} values. The demonstrated anti-HIV activity in the absence of any apparent toxicity to host cells shows these molecules to have an impressive selectivity and makes them attractive candidates for further study. Of equal interest is the puzzle of how the racemic litseaverticillols (**1**–**8**) are derived in the natural environment. Racemic mixtures are highly atypical of natural products, whose syntheses are usually templated by homochiral enzymes. Herein, we provide a potential answer to this dichotomy in the form of a proposed biomimetic synthesis that delivers litseaverticillols A (**1**) and C (**3**) as the products of a one-pot, five-operation cascade sequence beginning with an achiral precursor and initiated by a cycloaddition reaction involving singlet oxygen ($^1O_2$).[3] Further support for the biogenetic hypothesis is garnered from the subsequent elaboration of litseaverticillol A through singlet-oxygen-mediated transformations to afford three additional family members.



Scheme 1. Structures of litseaverticillols A–H.

Careful examination of these structurally related sesquiterpenes revealed that litseaverticillols D–H (**4**–**8**) could arise from direct oxidation of the first-generation litseaverticillols A–C (**1**–**3**). For example, litseaverticillols D, F, and G are the three possible products that can be derived from an ene reaction with $^1O_2$[4] at the side-chain double bond most distal to the cyclopentenone ring in litseaverticillol A (Scheme 2). In a similar manner, litseaverticillol B could be expected to be the precursor to litseaverticillol E, while litseaverticillol H may represent the oxidation product of both litseaverticillols F and G. This proposed biogenetic origin of the litseaverticillols D–H is in full accord with the high natural abundance of the three components necessary for the photochemical formation of highly reactive singlet oxygen, which are: a) molecular dioxygen (ca. 20% in atmospheric air),



Scheme 2. Retrosynthetic analysis and strategy.

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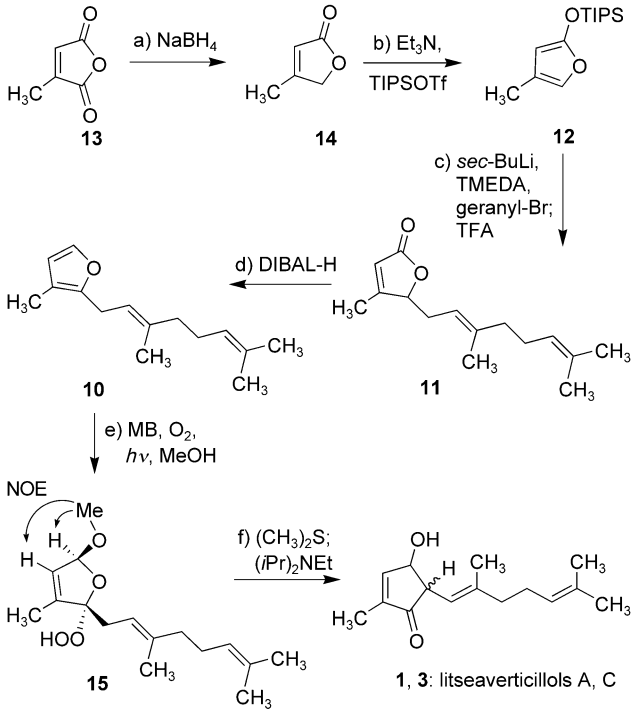
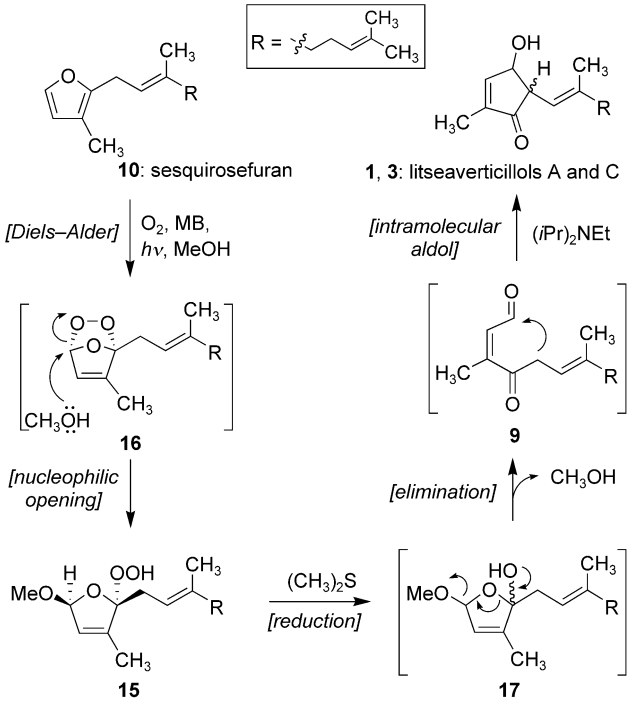
b) photosensitizers such as tannins and chlorophylls, and c) visible light.

We envisioned that the first generation listeaverticillols A–C might be derived from keto aldehyde **9** (an achiral precursor) through an intramolecular aldol reaction in a scenario that is proposed to mimic the natural nonenzymatic biogenesis and is consistent with the fact that compounds **1**–**8** were isolated as racemates (see above and Scheme 2). In turn, we anticipated that ketoaldehyde **9** could arise from the naturally occurring sesquirosefuran (**10**)[5] through a chemoselective $^1O_2$ oxidation of its furan moiety.[6] Finally, sesquirosefuran (**10**) might be synthesized by alkylation of the known furan **12**.[7]

The clear strategy that emerged from our retrosynthetic analysis enabled us to embark on the synthetic phase of the investigation. Furan derivative **12** was easily prepared by using a known two-step procedure[7,8] that begins with commercially available and inexpensive citraconic anhydride (**13**; Scheme 3). *Ortho*-metalation of **12** with *sec*-butyllithium followed by alkylation of the resultant anion with geranyl bromide and in situ acidic hydrolysis of the triisopropylsilyl ether moiety afforded lactone **11**. When DIBAL-H (1.7 equiv) was employed[9] as the reducing agent for lactone **11**, accompanied by an acidic work-up (10% HCl), sesquirosefuran **10** could be obtained in 85% yield (Scheme 3). This efficient transformation (**11**→**10**) prompted us to turn our attention towards accomplishing the direct oxidation of sesquirosefuran (**10**) to obtain keto aldehyde **9**. A serious obstacle to this process was expected to be the concomitant, if not faster, oxidation of the double bonds present in the appended side chain of **10**. Indeed, application of literature protocols for the direct oxidation of furans to *cis*-1,4-enediones, which involve treatment with magnesium monoperoxyphtalate[10] and Br_2/MeOH/dilute H_2SO_4,[11] led to rapid epoxidation and bromination, respectively, of the side-chain double bonds of **10**. These failures led us to examine the application of the pioneering work of Foote and Schenck[12] for the photosensitized oxygenation ($^1O_2$) of alkyl-substituted furans. The conditions used in this approach are also closer to the original biomimetic proposal. The photoinduced oxidation of the furan moiety of sesquirosefuran (**10**; 30 s irradiation with visible light of a methanolic solution bubbled through with O_2 and containing 10^{-4} M methylene blue as photosensitizer) led to the quantitative and exclusive formation of adduct **15**. The structure of hydroperoxide **15** was confirmed by NOE experiments (Scheme 3) and was found to be the opposite regioisomer to that proposed for the photooxidation of 2-methylfuran and menthofuran in MeOH.[12] Hydroperoxide **15** was treated with 5.0 equivalents $(CH_3)_2S$ in $CDCl_3$ and the reaction monitored by ^1H NMR spectroscopy. Complete reduction of **15** to a mixture of diastereomeric hemiacetals (**17**, Scheme 4) was observed after 2 h stirring at room temperature. At the same time, a substantial amount of the keto aldehyde **9** was observed. Futhermore, prolonged stirring of this solution (3 h more) at room temperature afforded keto aldehyde **9** in high yield (90%), accompanied



Scheme 3. Biomimetic total synthesis of litseaverticillols A and C. Reagents and conditions: a) Ref. [8]; b) Et_3N (1.4 equiv), TIPSOTf (1.2 equiv), CH_2Cl_2, 0→25 °C, 6 h, 81%; c) TMEDA (1.8 equiv), *sec*-BuLi (1.8 equiv), THF, 0 °C, 2 h, geranyl-Br (2.0 equiv), 0 °C, 3 h; then TFA (5.0 equiv), 25 °C, 1 h, 63%; d) DIBAL-H (1.7 equiv), THF, −78→−5 °C, 3 h, 85%; e) MB (10^{-4} M), O_2 (bubbling), MeOH, *hν*, 0 °C, 30 sec, 97%; f) $(CH_3)_2S$ (5.0 equiv), $CHCl_3$, 25 °C, 5 h; then $(iPr)_2NEt$ (1.0 equiv), 25 °C, 4 h, 55% **1**/**3** (19:1). TIPSOTf = triisopropylsilyl trifluoromethanesulfonate; TMEDA = *N,N,N′,N′*-tetramethylethylenediamine; THF, tetrahydrofuran; TFA = trifluoroacetic acid; DIBAL-H = diisobutylaluminium hydride; MB = methylene blue.



Scheme 4. Mechanistic rationale for the tandem tranformation of sesquirosefuran to litseaverticillols A and C.

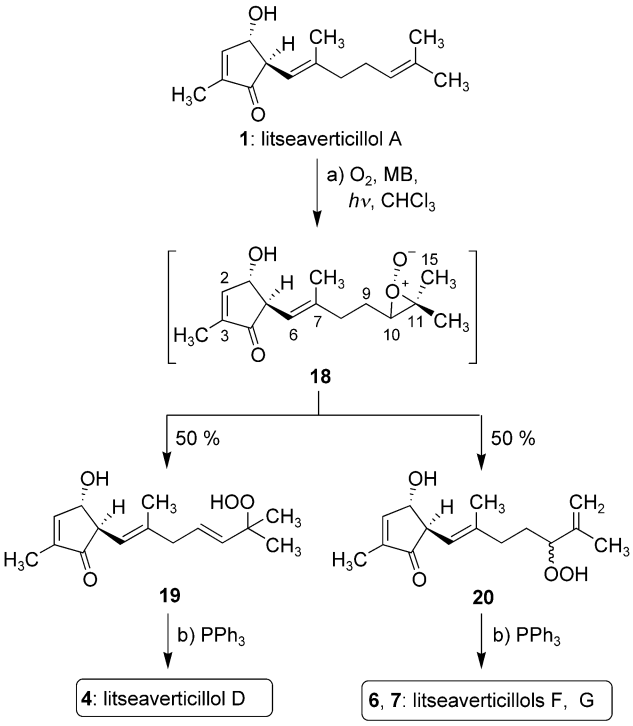
by just 10% unidentified byproducts. In situ treatment of the solution of keto aldehyde **9** with $(i\text{Pr})_2\text{NEt}$ (1.0 equiv), 4 h stirring, and subsequent chromatographic purification gave a 19:1 mixture of litseaverticillols A (**1**) and C (**3**) in 53% overall yield from sesquirosefuran **10**.

Keto aldehyde **9** is a labile compound and decomposed completely upon standing for two days. However, premature addition of Hünig's base before the complete disappearance of hemiacetals **17** (7:3 mixture of **17**/**9**) suppressed the elimination of MeOH and led to a 7:3 mixture of **17**/**1**. This ratio remained unchanged even after three days at room temperature. Only replacement of the solvent (MeOH) with CH_2Cl_2 or $CHCl_3$ prior to the addition of $(CH_3)_2S$ was necessary for the entire one-pot, five-operation sequence (**10**→**1** and **3**).

A detailed mechanistic rationale for this tandem sequence transforming sesquirosefuran (**10**) to litseaverticillols A (**1**) and C (**3**) is given in Scheme 4. The first step involves the [4+2] cycloaddition of singlet oxygen to the furan moiety[13] of **10** and is followed by regio- and diastereoselective[14] nucleophilic opening of endoperoxide **16** by MeOH. Reduction of the resulting hydroperoxide **15** to the fleeting anomeric hemiacetals **17** leads to the achiral keto aldehyde **9**, after elimination of MeOH. The final step is a base-induced intramolecular aldol reaction of the labile keto aldehyde **9** to form a 19:1 thermodynamic mixture of litseaverticillols A (**1**) and C (**3**).

With the synthesis of litseaverticillol A (**1**) secured, the stage was set for the application of a second type of singlet-oxygen reaction. Visible light irradiation of a solution of **1** in $CDCl_3$ (10^{-4} M methylene blue) bubbled through with O_2 for 2 min at 0°C afforded an equimolar mixture (^{1}H NMR analysis) of tertiary hydroperoxide **19** and diastereomeric secondary hydroperoxides **20** (Scheme 5). In situ reduction of this mixture with PPh_3 instantaneously produced the corresponding naturally occurring diols litseaverticillol D (**4**) and litseaverticillols F (**6**), and G (**7**), which were separated by flash chromatography. Like synthetic litseaverticillols A (**1**) and C (**3**), the litseaverticillols D (**4**), F, and G (**6** and **7**) derived from the above procedure were shown to be identical to the natural substances[1] by IR, ^{1}H NMR, ^{13}C NMR, and HRMS analyses. Only trace amounts of a more polar mixture of triols resulting from oxidation of both side-chain double bonds were isolated under the reaction conditions used (2 min irradiation at 0°C). The regioselective oxidation of one of the three trisubstituted double bonds of **1** occurs for a combination of electronic and steric reasons:[15] the C10=C11 double bond is more accessible to the electrophilic $^1O_2$ than C6=C7, and the C2=C3 bond is electron deficient. The equimolar formation of the tertiary and secondary allylic hydroperoxides (**19** and **20**) is consistent with the formation of intermediate perepoxide **18**[16] (Scheme 5), in which the negatively charged oxygen atom is directed towards the more-substituted side of the previously present double bond (*cis* effect).[17] Allylic hydrogen abstraction from C9 and C15 of perepoxide **18** results in balanced formation of the ene reaction products, allylic hydroperoxides **19** and **20**.

In conclusion, we have developed a fast and reliable synthesis for the laboratory preparation of this new and biologically promising class of natural products by using a sequence of reactions proposed to be biomimetic. This initially convergent route provides the first generation of litseaverticillols A (**1**) and C (**3**) in four steps with an overall yield of 29% (starting from known furan **12**), and then diverges at this late stage to allow the preparation of the second-generation litseaverticillols D (**4**), F (**6**), and G (**7**). The developed technology should be easy to adapt for the synthesis of litseaverticillols B (**2**) and E (**5**) by replacing geranyl-Br with neryl-Br in the alkylation step (Scheme 3). This route will be utilized for the synthesis of selected analogues for further chemical biology studies.[18] For example, based on our proposed biomimetic synthesis, we believe that the $\Delta^{6,7}$ *Z*-geometrical isomers of litseaverticillols F and G (**6** and **7**) exist in nature, despite the fact that they have not yet been isolated. It is important to test the anti-HIV activity of these analogues since it has been shown that a change in configuration at $\Delta^{6,7}$ from *E* to *Z* generates a two- to threefold enhancement in activity when comparing **1** and **4** with **2** and **5**, respectively.[1] Perhaps, most significantly, these studies add considerably to the scope of syntheses employing different modes of singlet-oxygen reactions as a means to mimic nature in the construction of natural products.



Scheme 5. Biomimetic transformation of litseaverticillol A into litseaverticillols D, F, and G through a regioselective singlet-oxygen-ene reaction. Reagents and conditions: a) MB (10^{-4} M), O_2 (bubbling), $CHCl_3$, *hν*, 0°C, 2 min; b) PPh_3 (2.0 equiv), $CHCl_3$, 25°C, 5 min, 35% **4** plus 35% **6** and **7** over 2 steps.

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