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Biomimetic Total Synthesis of Litseaverticillols B, E, I, and J and Structural Reassignment of Litseaverticillol E

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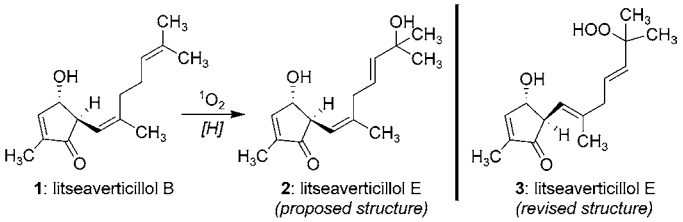
ABSTRACT



The first total synthesis of litseaverticillols B (1), E (2), I (4), and J (5) as well as the structural reassignment of litseaverticillol E (2) have been achieved by means of a biomimetic sequence of transformations during which a [4 + 2]-initiated reaction cascade and an ene reaction, both involving singlet oxygen ($^1O_2$), formed key steps. The reassignment of the structure of litseaverticillol E (3) to include an allylic hydroperoxide provides strong support for our biogenetic hypothesis.

In 2001, the first[1] of a series of papers[2] was published which together disclosed the structures of an entire family of novel and newly isolated sesquiterpenes, the litseaverticillols. These natural products immediately sparked our interest, not only because they exhibited potent and selective anti-HIV activity but also because close examination of their structures suggested to us an interesting hypothesis regarding their biogenesis. Thus inspired, we set forth on a program directed toward the total syntheses of the entire family of compounds and analogues thereof. Herein, we report a reassignment of structure for litseaverticillol E resulting from our total synthesis of the so-called second-generation litseaverticillols derived from litseaverticillol B (**1**, Figure 1). These syntheses lend considerable weight to our proposal regarding the biogenesis of these compounds (Scheme 1).

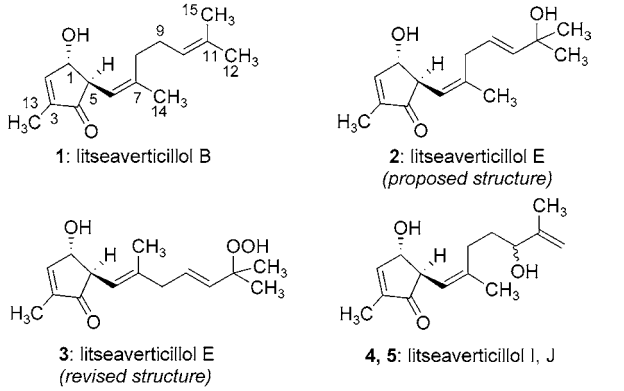


Figure 1. Structures of litseaverticillol B with its second-generation congeners, litseaverticillols E, I, and J.

(1) Zhang, H.-J.; Tan, G. T.; Hoang, V. D.; Hung, N. V.; Cuong, N. M.; Soejarto, D. D.; Fong, H. H. S.; Pezzuto, J. M. *Tetrahedron Lett*. **2001**, *42*, 8587−8591.

(2) (a) Hoang, V. D.; Tan, G. T.; Zhang, H.-J.; Tamez, P. A.; Hung, N. V.; Xuan, L. X.; Huong, L. M.; Cuong, N. M.; Thao, D. T.; Soejarto, D. D.; Fong, H. H. S.; Pezzuto, J. M. *Phytochemistry* **2002**, *59*, 325−329. (b) Zhang, H.-J.; Tan, G. T.; Hoang, V. D.; Hung, N. V.; Cuong, N. M.; Soejarto, D. D.; Pezzuto, J. M.; Fong, H. H. S. *Tetrahedron* **2003**, *59*, 141−148.

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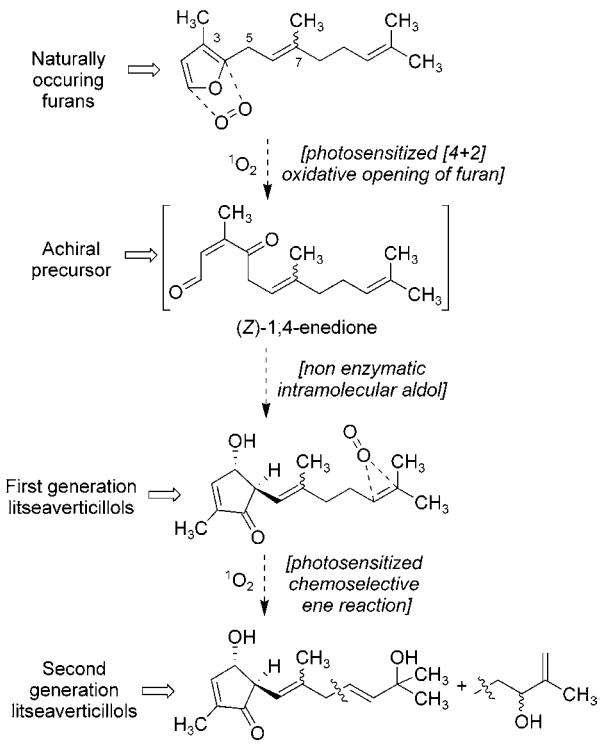
Scheme 1. Our Proposed Biogenesis of the Litseaverticillol Family



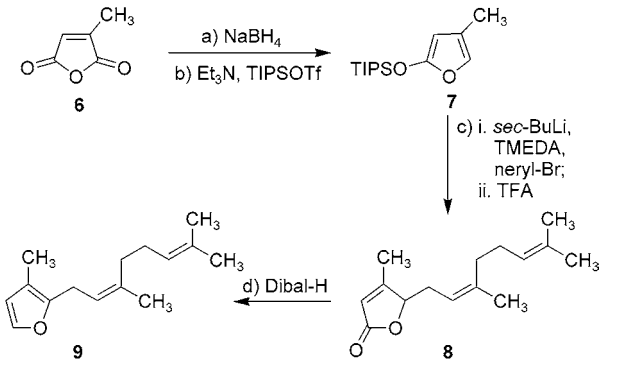
The litseaverticillols are a family of racemates; this characteristic is relatively rare in natural products and is suggestive of a nonenzymatic biosynthesis from an achiral precursor. They were isolated from the leaves and twigs of a perennial shrub, *Litsea verticillata* Hance, which grows in the Ninh Binh Province of Vietnam. It is well-known that one fundamental element of phytochemistry relates to the ready availability in plant matter of all three components required for the promotion of singlet oxygen transformations. Air containing molecular dioxygen (20%), a proliferation of photosensitizers (such as chlorophyll), and copious amounts of visible spectrum light together conspire to make the excitation of molecular dioxygen to singlet oxygen, followed by reaction of this highly reactive species with proximal double bonds, a frequent occurrence.[3]

It is our proposal that the litseaverticillols are the products of a cascade initiated by just such a photochemical reaction (Scheme 1). Thus, we propose that naturally occurring furans (e.g., sesquirosefuran[4]) undergo a [4 + 2] cycloaddition with singlet oxygen thereby initiating a cascade which affords the respective labile (*Z*)-1,4-enedione.[5] This newly formed enedione may then undergo an intramolecular aldol to furnish a mixture of $\Delta^{6,7}$-geometric isomers, the first generation litseaverticillols. This particular step is discussed in more detail later in the report. The second-generation litseaverticillols may then arise from the first generation compounds through a second singlet oxygen reaction; this time the mode is an ene reaction.[6]

We had previously reported our success in applying a general strategy derived from this proposal to the total synthesis of litseaverticillol A (**17**) and its C_1 diastereoisomer litseaverticillol C, as well as the offspring of the former molecule.[7] Recently, we switched our focus onto litseaverticillol B (**1**) and its close congeners in hopes of completing the syntheses of the series of naturally occurring litseaverticillols and selected analogues. The analogues we initially chose to target (**4** and **5**) incorporated structural features which had been identified as pivotal to the compound's anti-HIV activity and selectivity in the previously reported structure activity relationship (SAR) data.[2b] In the process of completing their synthesis we have uncovered a number of important observations related to this family, not least of which is the mistaken structural assignment (**2**) originally published for litseaverticillol E (**3**).[2b]

Our first task when targeting litseaverticillol B (**1**) was the preparation of the precursor for the singlet oxygen chemistry, furan **9**, which was achieved as shown in Scheme 2. Thus, commercially available and cheap citraconic anhydride (**6**) was converted into furan **7** by use of a known two-step procedure.[8,9] Subsequent *ortho*-metalation of **7** with *sec*-butyllithium, quench of the resultant anion with neryl bromide, and in situ hydrolysis of the TIPS ether assisted

Scheme 2. Preparation of Furan **9**[a]



[a] Reagents and conditions: (a) ref 9; (b) Et_3N (1.4 equiv), TIPSOTf (1.2 equiv), CH_2Cl_2, 0 → 25 °C, 6 h, 81%; (c) TMEDA (1.8 equiv), *s*-BuLi (1.8 equiv), THF, 0 °C, 2 h, neryl-Br (2.0 equiv), 0 °C, 3 h; then TFA (3.0 equiv), 25 °C, 1 h, 61%; (d) Dibal-H (1.7 equiv), THF, −78 → −5 °C, 3 h, 82%. TIPSOTf = triisopropylsilyltrifluoromethanesulfonate; TMEDA = *N*,*N*,*N*′,*N*′,-tetramethylethylenediamine; TFA = trifluoroacetic acid; Dibal-H = diisobutylaluminum hydride.

(3) For leading references regarding $^1O_2$ reactions with double bonds, see: (a) Wasserman, H. H.; Murray, R. W. *Singlet Oxygen*; Academic Press: New York, 1979; pp 287−427. (b) Stratakis, M.; Orfanopoulos, M. *Tetrahedron* **2000**, *56*, 1595−1615. (c) Clennan, E. L. *Tetrahedron* **2000**, *56*, 9151−9179.

(4) Hayashi, N.; Komae, H.; Eguchi, S.; Nakayama, M.; Hayashi, S.; Sakao, T. *Chem. Ind. (London)* **1972**, 572−573.

(5) Foote, C. S.; Wuesthoff, M. T.; Wexler, S.; Burstain, I. G.; Denny, R.; Schenk, G. O.; Schulte-Elte, K. H. *Tetrahedron* **1967**, *23*, 2583−2599.

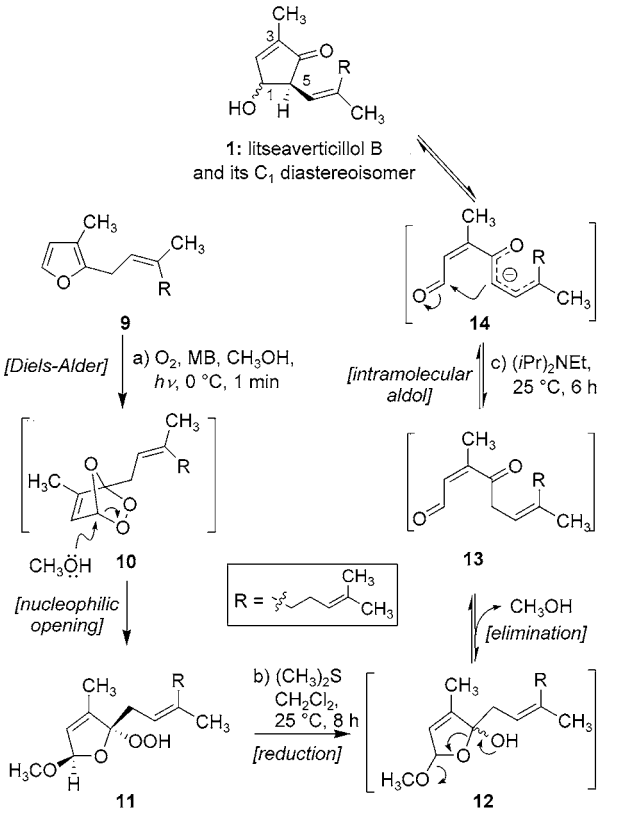
(6) For a selected review, see: Prein, M.; Adam, W. *Angew. Chem., Int. Ed.* **1996**, *108*, 519−538.

(7) Vassilikogiannakis, G.; Stratakis, M. *Angew. Chem., Int. Ed*. **2003**, *42*, 5465−5468.

(8) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc*. **1999**, *121*, 6990−6997.

by TFA, furnished the lactone **8**. Reduction of this lactone (**8**) with Dibal-H afforded a high yield of the desired furan **9**. Our previous experience synthesizing litseaverticillol A (17) gave us a set of ideal conditions for the furan oxidation cascade that followed. Thus, furan **9** became a willing partner in a [4 + 2] cycloaddition with singlet oxygen, generated by the methylene blue assisted photoexcitation of aerial molecular dioxygen. This reaction, undertaken in methanol as solvent, initially affords the fleeting endoperoxide adduct **10**, which is opened nucleophilically by the solvent to yield quantitatively and exclusively the hydroperoxide **11** (Scheme 3).

Scheme 3. Singlet Oxygen Initiated Cascade Transformation of Furan **9** into Litseaverticillol B: Mechanistic Rationale[a]



[a] Reagents and conditions: (a) MB (10^{-4} M), O_2 (bubbling), CH_3OH, *hν*, 0 °C, 1 min, 97%; (b) $(CH_3)_2S$ (5.0 equiv), CH_2Cl_2, 25 °C, 8 h; (c) $(i\text{-Pr})_2NEt$ (1.0 equiv), 25 °C, 6 h, 51% over two steps. MB = methylene blue.

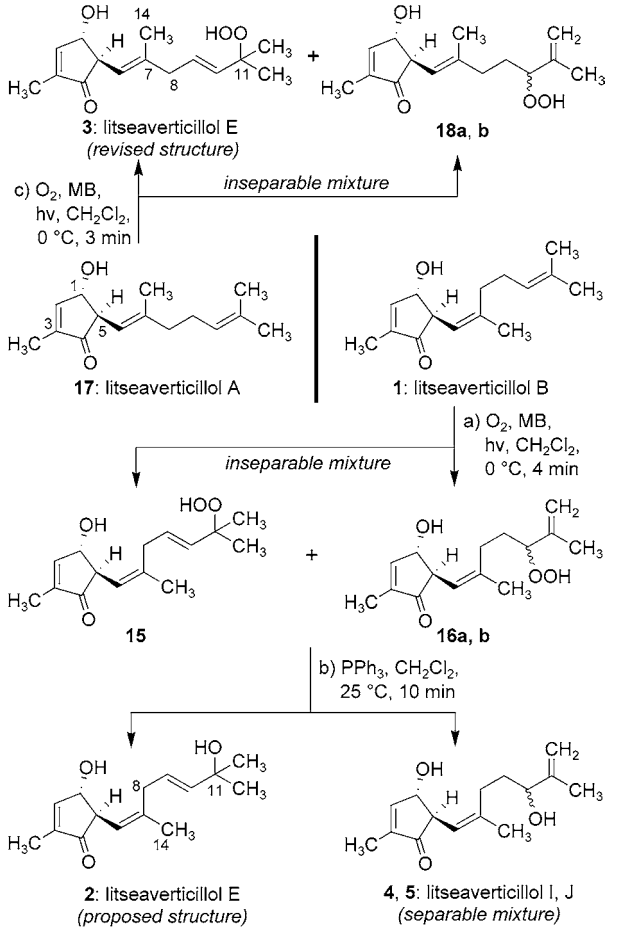
This hydroperoxide **11** has been isolated and fully characterized, but its preferred fate for our purposes is reduction, using excess dimethyl sulfide, to a mixture of diastereomeric hemiacetals **12**, ring opening elimination of methoxide to furnish the achiral (*Z*)-1,4-enedione **13**,[5] followed by base-induced intramolecular aldol reaction to directly afford litseaverticillol B (**1**) accompanied by trace amounts (5%) of its diastereoisomer at C_1. Crucially, if the cascade reaction mixture is left for prolonged periods in the presence of Hünig's base (12 h) then substantial amounts of the $\Delta^{6,7}$ geometrical isomer, litseaverticillol A (**17**, 15%), were isolated from the product mixture. Thus, litseaverticillol B (**1**) must undergo a retro-aldol reaction to regenerate **14** which can suffer one of two fates, either reversion to litseaverticillol B (**1**) or stereochemical scrambling and aldol reaction to afford litseaverticillol A (**17**). Spectroscopic data of synthetic litseaverticillol A (**17**) and B (**1**) were identical to those reported for the natural products.[2b] Since the starting furan (**9**) is geometrically pure, this stereochemical scrambling is a feature of the cascade itself. Presumably it is facilitated by the ready formation and extended conjugation of the anion **14**. Furthermore, it suggests that the entire litseaverticillols family may be derived from one naturally occurring furan, such as sesquirosefuran[4] bearing the less sterically hindered geranyl side-chain ($\Delta^{6,7}$ (*E*)-double bond). It should be noted that among the first-generation litseaverticillols the one bearing the least sterically encumbered arrangement about both the ring substituents (C_1 and C_5) and the $\Delta^{6,7}$ double bond, litseaverticillol A, is the most common member of this family of natural products.

With the total synthesis of litseaverticillol B (**1**) accomplished it appeared that all that remained was to investigate the synthesis of the second generation offspring of this natural product. To this end, we treated a solution of litseaverticillol B (**1**) in CH_2Cl_2 with singlet oxygen generated in situ using the previously established[7] optimal conditions shown in Scheme 4. Following the reduction of the mixture (**15**, **16a**, and **16b**) obtained from this chemoselective photochemical $^1O_2$-ene reaction with PPh_3, we were able to separate three products **2** (35%), **4** (22%), and **5** (18%). We choose to name compounds **4** and **5** litseaverticillols I and J, respectively. These isomers have not (yet) been isolated from a natural source, perhaps precisely because they are second-generation compounds arising from the side-chain oxidation of litseaverticillol B (**1**, sterically encumbered $\Delta^{6,7}$ (*Z*)-double bond) which was a minor component of the isolation mixture compared to litseaverticillol A (**17**, $\Delta^{6,7}$ *E*-double bond). These compounds had been targeted for synthesis because they combine the $\Delta^{6,7}$ (*Z*)-double bond with oxidation in the side chains; both these structural features had consistently improved the anti-HIV activity throughout the series of natural litseaverticillols.[2b] Results from ongoing biological investigations into these compounds will be reported in due course.

If we now refer back to the tertiary alcohol **2**, which we also synthesized when the side chain of litseaverticillol B (**1**, C_{10}═C_{11} double bond) was oxidized, its full spectral data did not match that of the natural product litseaverticillol E whose proposed structure it clearly possessed (Scheme 4). The structure of litseaverticillol E had caused the isolation group some concern as they discuss in one of their publications[2b] because a number of the peaks in the ^{13}C spectra were apparently incongruous with other litseaverticillols bearing comparable structural features to their pro-

(9) (a) Kayser, M. M.; Breau, L.; Eliev, S.; Morand, P.; Ip, H. S. *Can. J. Chem.* **1986**, *64*, 104−109. (b) Johnson, A. W.; Gowda, G.; Hassanali, A.; Knox, J.; Monaco, S.; Razavi, Z.; Rosebery, G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1734−1743. (c) Von der Ohe, F.; Brückner, R. *New J. Chem.* **2000**, *24*, 659−669.

Scheme 4. Singlet Oxygen Mediated Oxidation of Litseaverticillols A and B into the Second-Generation Litseaverticillols: Structural Reassignment of Litseaverticillol E[a]



[a] Reagents and conditions: (a) MB (10^{-4} M), O_2 (bubbling), CH_2Cl_2, *hν*, 0 °C, 4 min, 90%; (b) PPh_3 (2.0 equiv), CH_2Cl_2, 25 °C, 10 min, 35% of **2**, 22% of **4**, 18% of **5**; (c) MB (10^{-4} M), O_2 (bubbling), CH_2Cl_2, *hν*, 0 °C, 3 min, 92%.

posed structure. Specifically, they note that for litseaverticillol E the ^{13}C signals for C_8 and C_{14} are closer to those of the $\Delta^{6,7}$ (*E*)-isomers, and furthermore, they note the discrepancy wherein the C_{11} peak is shifted downfield from comparable peaks in other litseaverticillols. Taking into account our biogenetic hypothesis for the entire family, we began to suspect that the spectral and physical properties of litseaverticillol E might be more compatible with this compound being one of the intermediate hydroperoxides. The spectrum of natural litseaverticillol E was, however, distinctly different from each of the components of the mixture (**15**, **16a**, and **16b**) obtained on oxidation of litseaverticillol B (**1**), prompting us to reinvestigate the oxidation of litseaverticillol A (**17**). When the intermediate tertiary hydroperoxide **3**, obtained from the ene reaction of litseaverticillol A (**17**) with singlet oxygen, was isolated and fully characterized its data were found to match those of natural litseaverticillol E in every way. The initially inseparable mixture (**3**, **18a**, and **18b**) obtained on oxidation of litseaverticillol A (**17**) could be deconvoluted by selective reduction of the secondary hydroperoxides (**18a** and **18b**) with $(CH_3)_2S$ to afford litseaverticillols F and G.[2b,7] Under the reaction conditions employed (5.0 equiv Me_2S, 25 °C, 12 h) the tertiary hydroperoxide **3** remains unreacted.

In conclusion, we have completed the first total syntheses of litseaverticillols B (**1**), I (**4**), J (**5**), and E (**3**). As a result the structure of litseaverticillol E (**3**) has been revised. Litseaverticillol E (**3**) was found to be the relatively stable tertiary hydroperoxide product of an ene reaction of singlet oxygen with litseaverticillol A (**17**), thus providing strong evidence for our original biogenetic proposal. In the original assay litseaverticillol E (**3**) was not only one of the most potent anti-HIV litseaverticillols, but it exhibited the best selectivity among the surveyed natural products. Since we are now in command of all the facts regarding its structure, the desirable biological characteristics of litseaverticillol have prompted us to plan on making and testing further hydroperoxide analogues.

Acknowledgment. We thank Professor H. H. S. Fong for generously sharing relevant spectra with us. We thank Professor M. Stratakis for helpful discussions. This work was supported financially by the Greek Ministry of Education (B'EPEAEK, Pythagoras) and the European Science Foundation (ESF) Cost Action (Program D-28).

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra of compounds **1**, **2**, **3**, **4**, **5**, **8**, **9**, and **11** and the HRMS data for **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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