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Enantioselective Total Synthesis of Litseaverticillols A and B

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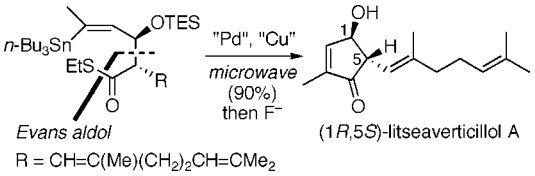
ABSTRACT



The first enantioselective total synthesis of the (1*R*,5*S*)-stereoisomer of litseaverticillols A and B, anti-HIV monocyclic sesquiterpenoids isolated from a perennial shrub found in Vietnam, was accomplished in six steps from homogeranic acid by employing the Evans asymmetric aldol reaction and a microwave-promoted cyclization of a stannylated thiol ester intermediate as the C–C bond-forming steps.

In the course of screening for anti-HIV natural products, Fong and co-workers isolated a novel class of sesquiterpenoids, litseaverticillols A (**1**) and B (**2**), along with their congeners [litseaverticillol C (5-*epi*-**1**) and litseaverticillols D−H (oxidation products at the C10−C11 olefinic portion of **1** or **2**)] from the leaves and twigs of the perennial shrub *Litsea verticillata* Hance, collected in Vietnam (Figure 1).[1]

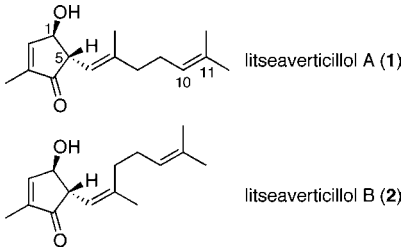


Figure 1. Structures of litseaverticillols A and B.

The monocyclic terpenes **1** and **2**, possessing a newly discovered carbon framework designated as litseane, exhibited considerably high anti-HIV activity (IC_{50}, 5.0 and 2−3 μg/mL, respectively) by inhibiting the replication of HIV-1, while showing cytotoxicity against HOG.R5 cells (a reporter cell line)[2] with CC_{50} values of 13.2 and 5.7 μg/mL, resepectively. Despite their unfavorable selectivity indices for more advanced in vivo studies (SI = CC_{50}/IC_{50}: 2.6 for **1** and 1.9−2.8 for **2**), the structural uniqueness of **1** and **2** as anti-HIV substances makes them attractive candidates for lead compounds to develop a new type of anti-HIV agents.[1,3] Quite intriguingly, the optical rotation values of these natural products (litseaverticillols A−H) were all found to be 0, which suggested that they were racemic mixtures, and this suggestion was confirmed by NMR analyses of the Mosher esters derived from litseaverticillols A, B, and D.[1] It is very unusual for organic molecules of biological origin to be obtained as racemic mixtures, since they are usually produced through a series of biotransformations catalyzed by homochiral enzymes. A plausible biosynthetic pathway of **1** via oxidative ring-closure of *cis*,*trans*-farnesyl diphosphate was proposed by Fong et al.[1] The pathway, however, does not seem to rationalize the formation of **1** as the racemate,

(1) (a) 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 Lett.* **2001**, *42*, 8587−8591. (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.

(2) Hoang, V. D.; Tan, G. T.; Zhang, H.-J.; Tamez, P. A.; Hung, N. V.; Cuong, N. M.; Soejarto, D. D.; Fong, H. H. S.; Pezzuto, J. M. *Phytochemistry* **2002**, *59*, 325−329.

(3) For recent reviews on anti-HIV natural products, see: (a) Asres, K.; Seyoum, A.; Veeresham, C.; Bucar, F.; Gibbons, S. *Phytother. Res.* **2005**, *19*, 557−581. (b) Singh, I. P.; Bharate, S. B.; Bhutani, K. K. *Curr. Sci.* **2005**, *89*, 269−290.

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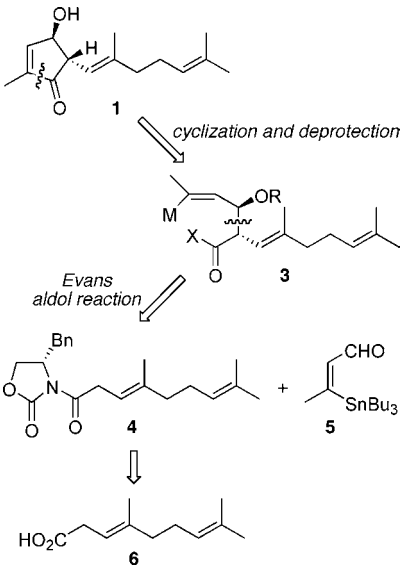
although it is quite reasonable as an ordinary terpenoid biogenesis. To interpret this puzzling observation, a series of elegant biomimetic synthetic studies on this class of sesquiterpenoids were conducted by Vassilikogiannakis and co-workers based on their insightful biogenetic hypothesis that litseaverticillols A−H might all be produced nonenzymatically from an achiral precursor such as naturally occurring sesquirosefuran through a cascade of reactions initiated with [4+2]-endoperoxide formation at the furan moiety by reaction with singlet oxygen generated photochemically by natural sensitizers such as porphyrins and tannins.[4] In line with this hypothesis, they achieved concise total syntheses of litseaverticillols A−G by employing singlet oxygen, generated by photoexcitation with methylene blue, for the [4+2]-oxidation of the furan ring of sesquirosefuran as well as for the oxidative ene reaction of the C10−C11 double bond on the side chain (to synthesize litseaverticillols D−G).[4] These synthetic studies successfully provided a clear explanation for the formation mechanism of all the members in the litseane family from the single achiral precursor (sesquirosefuran), including the isomerization mechanism of the geometry at the C6−C7 double bond.[4d,5]

We became interested in these racemic sesquiterpenes of medicinal interest from another viewpoint. We postulated that there could be a possibility that each enantiomer has different biological activity, namely the possibility that one enantiomer might have anti-HIV activity and the other cytotoxicity. In that case, the anti-HIV enantiomer with no cytotoxicity could be a promising lead compound for practical anti-HIV agents. This presumption prompted us to embark on the synthesis of the optically active forms of litseaverticillols. As part of our synthetic studies designed to probe the aforementioned possibility, we report herein the first enantioselective total synthesis of (1*R*,5*S*)-litseaverticillols A and B.

Our retrosynthetic analysis of (1*R*,5*S*)-litseaverticillol A (**1**) is shown in Scheme 1. We planned to obtain **1** by intramolecular nucleophilic substitution of **3** possessing an alkenylmetal moiety as the nucleophilic site and a carbonyl functionality connected to a leaving group (X) as the electrophilic site. A brief look at structure **3** made us envision the utilization of the Evans asymmetric aldol reaction[6] between oxazolidinone derivative **4** and stannylated aldehyde **5** for the installation of its β-alkoxy carbonyl portion in a stereocontrolled manner. Intermediate **4** would be readily obtainable from homogeranic acid **6**,[7] and aldehyde **5** had previously been prepared from 2-butyn-1-ol through hydroalumination followed by in situ treatment with *n*-Bu_3-SnCl and subsequent oxidation.[8] Just by changing the starting (*E*)-carboxylic acid into its (*Z*)-isomer, we should be able to obtain (1*R*,5*S*)-**2**. In our actual synthesis described below, we employed a 3:1 mixture of (*E*)- and (*Z*)-**6** obtained readily from geranyl bromide in two steps (nucleophilic substitution with NaCN followed by alkaline hydrolysis),[7] since it was difficult, in our hands, to obtain reproducibly high yields of geometrically pure (*E*)- and (*Z*)-homogeranic acid (**6**).[9] This compromise, however, had the fortunate outcome that both **1** and **2** could be obtained in a single synthetic pathway through separation of an intermediate *E*/*Z* mixture.

Scheme 1. Retrosynthetic Analysis of (1*R*,5*S*)-Litseaverticillol A (**1**)



In line with the synthetic plan, a 3:1 *E*/*Z* mixture of **6** was transformed into the corresponding oxazolidinone derivative **4** (Scheme 2). The *syn*-selective Evans aldol reaction of **4** with aldehyde **5** gave a mixture of two aldol products, **7** and **8**, which could quite fortunately be separated by repeated silica gel column chromatography to deliver (*E*)-isomer **7** and (*Z*)-isomer **8** in isolated yields of 34% and 10%, respectively, reflecting the geometrical ratio of the starting carboxylic acid **6**. To effect the key conversion of **7** into **11**, we first attempted Li−Sn exchange-mediated direct cyclization of the stannylated oxazolidinone derivative **7** via alkenyllithium intermediate **10** (Scheme 3). This reaction, however, afforded only a complex mixture despite extensive examination of reaction conditions. Circumvention through vinyl iodide **9** obtained from **7** by Sn−I exchange reaction was also unsuccessful, resulting again in the formation of a complex mixture. These results made us seek an alternative protocol for the formation of the cyclic enone **11**.

It has recently been reported by Liebeskind et al. that thiol esters can be transformed into ketones by reaction with aryl-

(4) (a) Vassilikogiannakis, G.; Stratakis, M. *Angew. Chem.* **2003**, *115*, 5620−5622. (b) Vassilikogiannakis, G.; Stratakis, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5465−5468. (c) Vassilikogiannakis, G.; Margaros, I.; Montagnon, T. *Org. Lett.* **2004**, *6*, 2039−2042. (d) Vassilikogiannakis, G.; Margaros, I.; Montagnon, T.; Stratakis, M. *Chem. Eur. J.* **2005**, *11*, 5899−5907.

(5) For a review on biomimetic cascade reactions in organic synthesis, see: Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551−564.

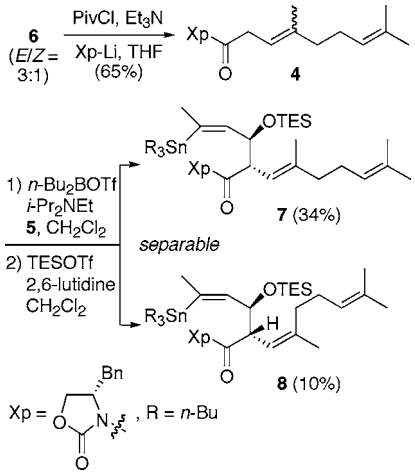
(6) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129.

(7) Mori, K.; Y. Funaki *Tetrahedron* **1985**, *41*, 2369−2377.

(8) (a) Domínguez, B.; Pazos, Y.; de Lera, A. R. *J. Org. Ghem.* **2000**, *65*, 5917−5925. (b) Evano, G.; Schaus, J. V.; Panek, J. S. *Org. Lett.* **2004**, *6*, 525−528.

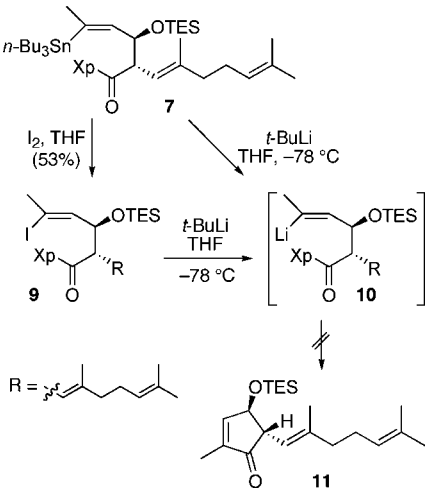
(9) Yanagisawa, A.; Yasue, K.; Yamamoto, H. *Org. Synth.* **1997**, *74*, 178−186.

Scheme 2. Preparation of Cyclization Precursors **7** and **8**



or alkenylboronic acids,[10] or with aryl-, alkenyl-, or allylstannanes[11] in the presence of an appropriate palladium catalyst and Cu(I) additive. Although these reactions had not been applied to intramolecular cases to form cyclic ketones such as **11**, their generality and mild reaction conditions

Scheme 3. Attempted Cyclization via Alkenyllithium Intermediate **10**



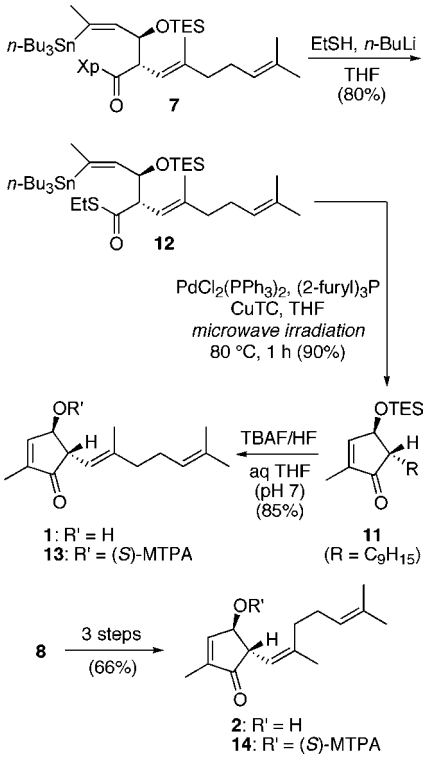
prompted us to examine the new methodology. Thus, the oxazolidinone derivative **7** was first converted into the corresponding thiol ester **12**,[12] and then subjected to the ring closure reaction by using a variety of palladium catalysts and Cu(I) additives (Scheme 4). After investigations of several reaction conditions, it was found that the cyclization of **12** to **11** could be achieved in 63% yield by stirring at 50

(10) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260−11261.

(11) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033−3035.

(12) Miyazaki, T.; Han-ya, Y.; Tokuyama, H.; Fukuyama, T. *Synlett* **2004**, 477−480.

Scheme 4. Synthesis of (1*R*,5*S*)-Litseaverticillols A (**1**) and B (**2**)



°C for 2 days in THF in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$, 0.4 equiv of $(2\text{-furyl})_3P$, and 4.5 equiv of Cu(I) thiophene-2-carboxylate (CuTC). Furthermore, this conversion was revealed to be accelerated by microwave irradiation at 80 °C to afford **11** within 1 h in an improved yield of 90%.[13] Finally, removal of the TES-protecting group by treatment of **11** with a mixture of TBAF and HF (adjusted to pH 7 to prevent possible loss of stereochemical integrity via a retroaldol−aldol process or keto−enol equilibration), furnished 85% yield of (1*R*,5*S*)-litseaverticillol A (**1**), $[\alpha]^{24}_D$ −122 (*c* 0.10, $CHCl_3$). By following the same three-step sequence of reactions as employed for the conversion of **7** into **1**, (*Z*)-cyclization precursor **8** was transformed into (1*R*,5*S*)-litseaverticillol B (**2**) in 66% yield over the three steps, $[\alpha]^{24}_D$ −151 (*c* 0.10, $CHCl_3$). Derivatization of **1** and **2** into the corresponding (*S*)-MTPA esters (**13** and **14**, respectively) followed by comparison of their ^{1}H NMR spectra with those of MTPA esters prepared by Fong et al. from racemic **1** and **2**[1] confirmed that our synthetic materials were both ca. 98% ee. Careful inspection of the ^{1}H NMR spectra of **1** and **2**, however, indicated the presence of small amounts of the corresponding 1,5-*cis*-isomers (ca. 5% for **1**, and ca. 2% for **2**). These small degrees of epimerization during the final deprotection step are considered to have occurred through the keto−enol tautomerization rather than the retroaldol−aldol process, since the enantiomeric excesses

(13) For a review on mirowave chemistry, see: Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250−6284.

of **1** and **2** were both kept at a high level (98% ee) as mentioned above.

In conclusion, the enantioselective total synthesis of (1*R*,5*S*)-litseaverticillol A (**1**) and (1*R*,5*S*)-litseaverticillol B (**2**) was accomplished in six steps from homogeranic acid by employing the Evans asymmetric aldol reaction between oxazolidinone derivative **4** and stannylated aldehyde **5**, and the microwave-promoted cyclization of stannylated thiol ester intermediate **12** in the presence of $PdCl_2(PPh_3)_2$, $(2\text{-furyl})_3P$, and CuTC, as the C−C bond-forming steps. The synthesis of *ent*-**1** and *ent*-**2**, as well as the optically active forms of litseaverticillols C−H, is currently in progress.

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Supporting Information Available: Experimental procedures and copies of NMR spectra for compounds **1**, **2**, **4**, **7**, **8**, **11**, **12**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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